SM

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/310,638	05/12/1999	HERMONA SOREQ	2391.00096	9102

7590 06/02/2004

JOHN P. WHITE
COOPER & DUNHAM LLP
1185 AVENUE OF THE AMERICAS
NEW YORK, NY 10036

EXAMINER	
CROUCH, DEBORAH	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 06/02/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/310,638	SOREQ ET AL.	
	Examiner	Art Unit	
	Deborah Crouch, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 January 2004*.

2a)☐ This action is **FINAL**. 2b)☑ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17,19-24,26 and 27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11-14,17,19,20,23,24,26 and 27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12 May 1999* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on January 30, 2004 has been entered. The arguments contained therein have been fully considered but are not persuasive.

In a review of the present amended claims in view of applicant's summation of the telephone conversation January 15, 2004, the examiner realized that the advice or agreement given to applicant in that conversation was in error. The rejections below address the amendments resulting from that conversation.

The terminal disclaimer filed on May 4, 2001 disclaiming the terminal portion of any patent granted on this application that would extend beyond the expiration date of U.S. Patent 5,932,780 has been reviewed and is accepted. The obviousness type double patenting rejection has been overcome.

Claim Rejections - 35 U.S.C. § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 11-14, 17-20, 23, 24 and 26 remain, and newly added claim 27 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for transgenic mice and frog tadpoles whose genomes comprise a transgene comprising a AChE promoter operatively linked to a DNA sequence encoding a splice variant of human AChE expressing AChE with acetylcholinesterase activity, wherein said sequence is expressed in

cells of said mouse and where said mouse or tadpole exhibits changes in its neuromuscular junction structure, and transgenic nonhuman mammals whose genome comprises a DNA sequence encoding a cholinesterase operably linked to a mammary gland promoter, where expression of the DNA sequence results in the production of detectable levels of enzymatically active in the milk of the mammal, does not provide enablement for the preparation and use of transgenic animals comprising any and all variants of said cholinesterase genes or assay systems of these animals for reasons presented in the office action mailed December 20, 2002. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

For reasons stated in the office action mailed December 2, 2000, the breath of animals versus mice or frog tadpoles in claims 11-14, 23 and 26, and the breadth of the transgene remains limited because, at the time of filing, the art as a whole recognized that the production of transgenic animals as a whole was unpredictable. Transgenic animals have within their cells cellular mechanisms, which prevent expression of the transgene, such as DNA methylation or deletion from the genome (Kappell et al (1992) Current Opinion in Biotechnology 3, 549, col. 2, parag. 2). In addition, the position effect and unidentified control elements also were recognized to cause aberrant expression (Wall (1996) Theriogenology 45, 61, parag. 2, line 9 to page 62, line 3). The elements of the particular construct used to make transgenic animals was held to be critical, and that they must be designed case by case without general rules to obtain good expression of a transgene; e.g., specific promoters, presence or absence of introns, etc. (Houdebine (1994) Journal of Biotechnology, constructs page 275, column 1, 1st paragraph). At the time of filing, it was regarded the art that one could not predict whether a transgene that is expressed in a mouse (or any other animal) will also be expressed efficiently in another animal. This lack of

predictability in expression across species is due at least in part to cis acting elements which interact with different trans-acting factors in these other species (Strojek and Wagner (1988) Genetic Engineering para. bridg. pages 238-239). The integration of a transgene into difference species of animal has been reported to given divergent phenotypes (Mullins et al (1993) Hypertension 22, page 631, col. 1, parag. 1, lines 14-17). Furthermore, it was disclosed that "[t]he use of nonmurine species for transgenesis will continue to reflect the suitability of a particular species for the specific questions being addressed, bearing in mind that a given construct may react very differently from one species to another." (Mullins et al (1996) J. Clinical Invest. , page S39, Summary). These teachings are more relevant in the instant application where the claims are broadly drawn to non-human mammals, which express a recombinant DNA expression vector encoding a variety of Che species and variants. The distance between species of mice and frog is too extreme to take that the results in mice and tadpole are predictive for the genus of non-human animal. Further, applicant made a frog tadpole, which is some preadult form of a frog, and not an adult frog. There is no evidence of record that an adult frog developed from the transgenic tadpoles. Because over expression of the transgene disrupted neuromuscular junctions, it is possible that the neurological defect was great enough that tadpoles died prior to developing into frogs.

Claims 11-14, 23 and 26 lack an enabled use. The specification requires a use beyond mere expression for the claimed animals. One use is as a model of neuromuscular junctions, which clearly requires that the expression of transgene results in a phenotype more than expression. The specification states that for this use the animal need to develop abnormal neuromuscular junction structure (specification, page 33, lines 10-18). The second use, is that of a bioreactor animal where expression is organ specific, that is expression of the encoded cholinesterase is in the mammary gland at sufficient quantities

for detection/isolation (specification, page 35, lines 27-33). Thus claims 11-14, 23 and 26 have no use in view of the specification.

Claims 11-14, 17-20, 23, 24, 26 and 27 lack enablement for the scope of chimeric animal. As the claims do not require that the expression vector be integrated into the genome, the claims encompass animals where the transgenic exists as an extrachromosomal structure. The production of such animals with any type of phenotype is unpredictable as protocols for producing such animals were not available in the art at the time of filing nor does the present specification provide any guidance to producing them. The only guidance in the present specification is that the animals contain the expression vector within their genome. Further, claims 11-13 are not enabled as claim 11 requires expression of the cholinesterase but there is no mention of a promoter. At the time of filing, operable linkage to a promoter was the only method of expressing a transgene taught by the art. The specification provides no guidance on other methods of expressing a transgene in a transgenic animal.

Claim 17 lacks enablement as the specification does not teach what conditions are required for the promoter to be "capable of" or "not capable of" expressing detectable amounts of cholinesterase.

Thus, at the time of filing the skilled artisan would have been required to engage in an undue amount of experimentation without a predictable degree of success to implement the claimed invention.

Applicant argues that they limited the claims to state that the transgenic animal expresses, in its somatic and germ cells, the nucleic acid at a higher level relative to a nontransgenic animal. Applicant argues that several methods for detecting expression are disclosed in the specification and gives tail DNA restriction analysis. These arguments are not persuasive.

There is no evidence that germ cells of the transgenic animals express the nucleic acid sequence encoding a Che. Even in the Xenopus examples, expression is observed only in developing embryos. In transgenic mammals, germline expression is not achieved without specific promoters, none of which have been described. Likewise, there is no evidence that every somatic cell expresses the transgene. The examiner believes that applicant means to say that the nucleic acid encoding a Che is in the genome of animal or the genome of the germ and somatic cells. Further, tail DNA analysis does not detect expression; it detects integration.

Applicant argues that the Soreq declaration, page 4, parag. 6 cite evidence published by others which supports her point that cholinesterase enzyme requires neither membrane structure nor glycosylation for activity. This argument is not persuasive.

The examiner did review these statements by declarant Soreq. However, they are not convincing because they do not address the predictability that each Che would be expressed sufficiently in tadpoles and mice to produce a useful developmental model.

Applicants arguments regarding the enablement of the bioreactor claims have not been addressed the rejections concerning these claims are new.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 11-14, 17-20, 23, 24, 26 and 27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 11, 17, 19, 23, 24 are confusing as they state cholinesterase or Che enzyme. This is redundant as "ase" means enzyme. Applicant should delete "enzyme" in these

claims. Also some claims use "cholinesterase" and some use "Che." Applicant should be consistent to avoid being confusing.

Claims 11 are confusing as they are not clear as to whether applicant means that the recombinant nucleic acid expression vector is part of the genome or if the vector is extrachromosomal. It is suggested that applicant rewrite the claims "a transgenic nonhuman animal whose genome comprises ..

Claims 11 (c), 13, 19 and 23 are unclear if the biologically active variants are active for the respective cholinesterase activities named. Any enzyme would read on 11 (c) as all enzymes have a biological activity of cleaving proteins.

Claim 11 is further confusing as to whether there is a promoter present. It is not clear how a protein will be produced if the nucleic acid is not operably linked to a promoter. In view of claim 14, which specifically states a promoter, this confusion is more pronounced.

Claim 14 is confusing as there is no listing of groups of promoters or what promoters constitute the group. Use of the phrase "selected from the group of" requires more than one product or there is no group. Perhaps applicant meant "and is a eukaryotic host cell compatible promoter."

Claim 17 is confusing as "capable of" indicates that the animal will not express the transgene under certain situations, but this is not defined in the claim. Claim 17 is further confusing as the phrase beginning with "which (i) is selected from ..." as more than being eukaryotic host cell compatible is required by the claim; the promoter must be active in mammary tissue or the claim is nonfunctional. Claim 17 is confusing as the claims states the vector "further comprises a promoter" that must be active a eukaryotic cell. However, as mentioned above claim 11 requires expression, and thus claim 11 has a promoter functional in a eukaryotic animal.

Claim 20 is confusing as to the meaning of "recombinantally-produced point mutation and deletion of one or more residues and mutations." The examiner does not comprehend this limitation.

Claim 24 lacks antecedent basis as claim 17 has no mention of "lactating."

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 11, 13 rejected under 35 U.S.C. 102(b) as being clearly anticipated by US Patent 4,736,866 issued April 12, 1988 (Leder).

Leder teaches transgenic mice comprising the myc oncogene (col. 5, line 38 to col. 6, line 31). As the myc oncogene is comprised of nucleotides A, T, C and G, any one nucleotide of the myc oncogene would read on any one nucleotide A, T, C and G of any "fragment" of SEQ ID NO: 1, 3 or 5. It is noted that the claims does not specify any characteristic of the "fragment." Thus one nucleotide equals a fragment of the claimed SEQ ID NO's. Thus, Leder's mouse clearly reads on the claimed animal as the mouse of Leder would contain a recombinant expression vector comprising a nucleic acid encoding at least a one nucleotide fragment that is also contained in mouse of claim 13.

Claims are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Verlander et al (1992) Proceed. Natl. Acad. Sci (USA) 89, 12003-12007.

Verlander teaches transgenic pigs expressing a DNA sequence encoding protein C operatively linked to a mammary gland promoter, where detectable levels of protein C are found in the milk of the pigs (abstract). As the claims state a biological activity of cholinesterase, and protein C is an enzyme with protein cleaving active, protein C is regard

as having a biologically active of cholinesterase. Thus, Verlander clearly anticipates the claimed invention.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deborah Crouch, Ph.D. whose telephone number is 571-272-0727. The examiner can normally be reached on M-Th, 8:30 AM to 7:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on 571-272-0408. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Deborah Crouch

Deborah Crouch, Ph.D.
Primary Examiner
Art Unit 1632

May 28, 2004